

Asthma due to inhaled chemical agents—tolylene di-isocyanate

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Summary

Four patients with asthma due to tolylene di-isocyanate (TDI) were tested by occupational type exposure to a polyurethane varnish and its 'TDI activator'. Late asthmatic reactions were given in two patients, the third gave an immediate reaction and the fourth gave a dual, immediate followed by late asthmatic, reaction. The reactions in the last two patients were inhibited by disodium cromoglycate. Two patients encountered the TDI in fumes from soldering polyurethane coated wire. The possibility of sensitization in conditions of limited exposure requires more frequent consideration as none of the four subjects tested gave histories of heavy exposure.

Introduction

The provocation of asthma in sensitized subjects by the inhalation of very low concentrations of isocyanate derivatives, particularly tolylene di-isocyanate (TDI), has been widely reported, mainly in factory workers, since the initial report by Fuchs & Valade (1951), and more recently in subjects exposed to them in domestic circumstances. Whilst TDI is an irritant, the evidence is strongly suggestive of an allergic mechanism in the production of asthmatic reactions in exposed and sensitized subjects. The nature of the bronchial reactions resemble the immediate, late and dual reactions demonstrable in allergy to fungi, e.g. *A. fumigatus*, avian allergens and house dust and *Dermatophagoides* spp. (Pepys *et al.*, 1968; McCarthy & Pepys, 1971; Booij-noord *et al.*, 1972). The presence of reaginic antibodies to TDI shown by PCA tests in the monkey and of complement fixing and other antibodies (Taylor, 1970; Konzen, Craft & Scheel, 1966); the provocation of asthma by inhalation of an aerosol mixture (Sweet, 1968) and the production of specific lymphoid cell transformation (Bruckner *et al.*, 1968) are suggestive evidence of an immunological basis for the clinical manifestations produced by exposure to TDI. The development of simple, safe, acceptable methods for establishing the specific etiological diagnosis of TDI sensitivity and for clinical proof of its relevance is described.

Materials and methods

Test materials and method of testing

All four patients were tested by exposure to a two-pot polyurethane varnish with its accompanying 'tolylene di-isocyanate (TDI) activator'. The subjects first applied the polyurethane varnish itself with a paintbrush to a wood surface in a small cubicle (Fig. 1) followed on another day by application in the same way of the polyurethane



Fig. 1. Demonstration of occupational type method of testing. Repeated application of varnish with and without 'TDI activator'.

varnish mixed immediately before the test with the 'TDI activator', and one of the patients was tested by the application of the activator itself on another day. The content of TDI in the air over a period of 1 hr was between 0.00173 and 0.0018 ppm as measured by the method of Meddle, Radford & Wood (1969). No TDI was measured in the air when the varnish without the activator was applied. The effects of inhalation of 20 mg disodium cromoglycate and of lactose placebo given 10 min before the challenges were studied.

One of the two subjects affected by fumes from soldering wire was also tested with the fumes from the solder, the resins and the polyurethane coated wire to which she was exposed at work.

Three non-exposed subjects, one with asthma and two healthy subjects, were exposed to the activated varnish for 60 min without symptoms or changes in pulmonary function.

Case histories

1. *Patient R.R.*, a male aged 26 years, was a boat builder by trade for 10 years, and had been using a 'two-pot system' of varnish over the previous 8 years. He developed chest symptoms for the first time 14 months before being seen in hospital. Initially he experienced cough and dyspnoea at night; these symptoms disappeared at weekends and when on holiday. Gradually over the next 12 months they became more severe, often occurring before he finished work. He noticed that his symptoms were related only to periods when the polyurethane two-stage varnish was being used. There was no history of febrile reactions or loss of weight. He had no family or personal history of atopy. He had owned two budgerigars for 2 years. Physical examination was normal.

Other investigations. Haemoglobin, white blood count, absolute eosinophil count and ESR were normal. The chest X-ray was normal. Prick tests to twenty-three common allergens and to avian allergens were negative. Precipitin tests to avian extracts were negative.

Pulmonary function tests

	Result	% Predicted
VC	4800 ml	121%
FRC	2730 ml	100%
TLC	5350 ml	108%
RV/TLC	13.2%	
FVC	4900 ml	123%
FEV ₁	4000 ml	
FEV ₁ /FVC	81.5%	
CO gas transfer factor (single breath)	29.5	110%
Airways resistance (LV) (body plethysmograph)	1.41 (2830 ml)	

Inhalation tests and results (Fig. 2)

The following exposure, occupational type, tests were made:

- (1) Polyurethane varnish for 60 min.
- (2) Polyurethane varnish plus 'TDI activator' for 60 min.
- (3) Polyurethane varnish for 60 min.
- (4) 'TDI activator' for 20 min.
- (5) Inhalation of 20 mg disodium cromoglycate 10 min before test with 'TDI activator' for 20 min.
- (6) Inhalation of 20 mg disodium cromoglycate 10 min before and at hourly intervals up to 8 hr after test with 'TDI activator' for 20 min.
- (7) Polyurethane varnish plus 'TDI activator' for 60 min.

Results

Tests 1 and 3 with the polyurethane varnish provoked no reactions and there was little diurnal variation in pulmonary function tests. Tests 2, 4, 6 and 7 in which the

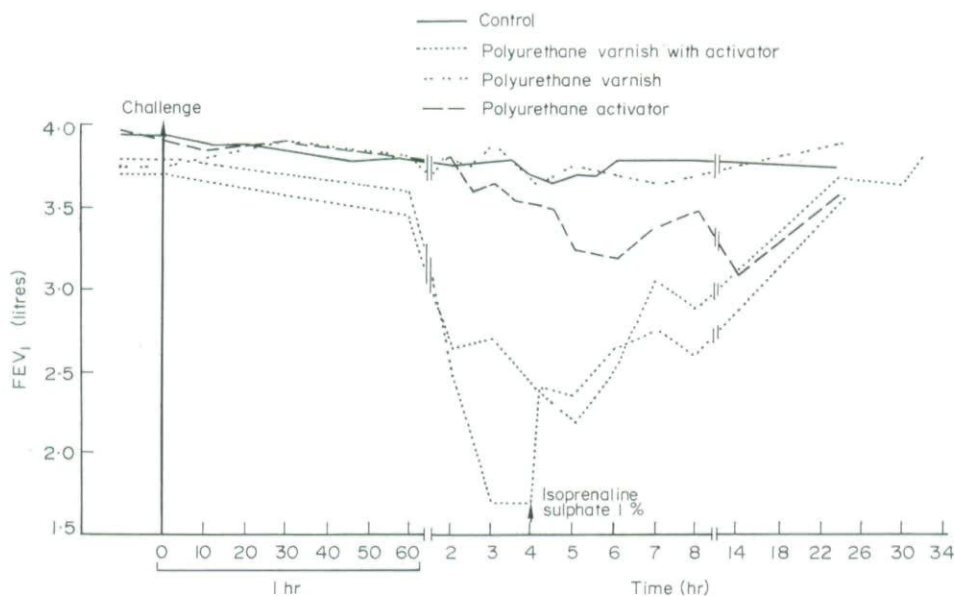


Fig. 2. Patient R.R. Occupational type exposure to components of two-stage polyurethane varnish. Note reproducible late asthmatic reactions.

TDI was present all provoked late asthmatic reactions which were not significantly modified by treatment with disodium cromoglycate.

The biggest falls in FEV_1 were produced by the challenges with the mixture of polyurethane varnish and 'TDI activator'. The timing of the bronchial reactions was taken from the end of the challenge period.

The bronchial reaction in tests 2 and 7 with the varnish plus TDI mixture appeared 1–2 hr after the test and was maximal at 3–4 hr, with a return to initial values at 24 hr. On examination at the height of the reaction wheezing rhonchi only were present.

White blood cell count and wet absolute eosinophil count (in parentheses)

Challenge	'Baseline'	6 and 8 hr
1		NA
2	5800 (460)	6600 (150)
3	5000 (190)	NA
4	5700 (180)	4800 (100)
5	4800 (120)	6300 (180)
6	6500 (170)	6400 (350)
7	5700 (200)	6900 (370)

2. *Patient L.E.*, a 46-year-old male who was a millwright by trade, was employed as a maintenance engineer for 8 years in a factory making refrigerators. This included the maintenance of polyurethane foam machines fitted with exhausts because of the hazards of TDI exposure. He had not to his knowledge ever been exposed to a 'spill' of TDI. He first developed symptoms of chest tightness and shortness of breath while at work $2\frac{1}{2}$ years before the present investigation. These symptoms were initially

mild, occurring only at work, and then only on a single day every 2-3 months. They resolved completely within 20 min of leaving work. Six months after the onset of these symptoms, while working above a functioning polyurethane foam machine, he experienced a severe attack of wheezing and breathlessness, lasting for 2 hr. From that time on he was aware of persistent mild wheezing and breathlessness occurring chiefly at night. He continued work with these symptoms for the following 12 months but avoided all maintenance work on the foam machines although working in the same building. He was then moved to a new area, a paint and assembly shop. After 1 month, although not knowingly in contact with any polyurethane products, he developed symptoms of severe asthma, requiring treatment with corticosteroids. Over the following 3 months he lost 1 month's work through this illness. From March 1971 there was a gradual improvement in his symptoms and at the time of examination he had only occasional bouts of wheezing. Two months prior to admission he spent 4 min 2 yd away from a working foam machine and within 5 min experienced marked chest tightness which resolved over the following hour. He had no family or personal history of atopy and at the time of investigation was asymptomatic.

On examination. Apart from a few scattered expiratory rhonchi there were no abnormalities.

Other investigations. Haemoglobin, white blood count, absolute eosinophil count and ESR were normal. Plasma proteins and electrophoretic strip were within normal limits. Chest X-ray was normal. Prick tests to twenty-one common allergens were negative.

Pulmonary function tests

	Result	% Predicted
VC	4800 ml	114%
FVC	4800 ml	114%
FEV ₁	3800 ml	113%
FEV ₁ /FVC	79%	
CO gas transfer factor (single breath)	40.7	158%

Inhalation tests

The following exposure, occupational type, tests were made. All of the tests were for a period of 30 min.

- (1) Polyurethane varnish.
- (2) Polyurethane varnish mixed with 'TDI activator'.
- (3) Inhalation of 20 mg disodium cromoglycate 10 min before challenge with polyurethane varnish plus 'TDI activator'.
- (4) Inhalation of 20 mg lactose 10 min before challenge with polyurethane varnish plus 'TDI activator'.

Results (Fig. 3)

Test 1 with the polyurethane varnish provoked no reactions and there was no marked diurnal variation in pulmonary function. Tests 2 and 4 with the mixture of polyurethane varnish and 'TDI activator' provoked immediate asthmatic reactions, maximal in 10-20 min and resolving in 1 hr. This reaction was completely inhibited by pretreatment with disodium cromoglycate.

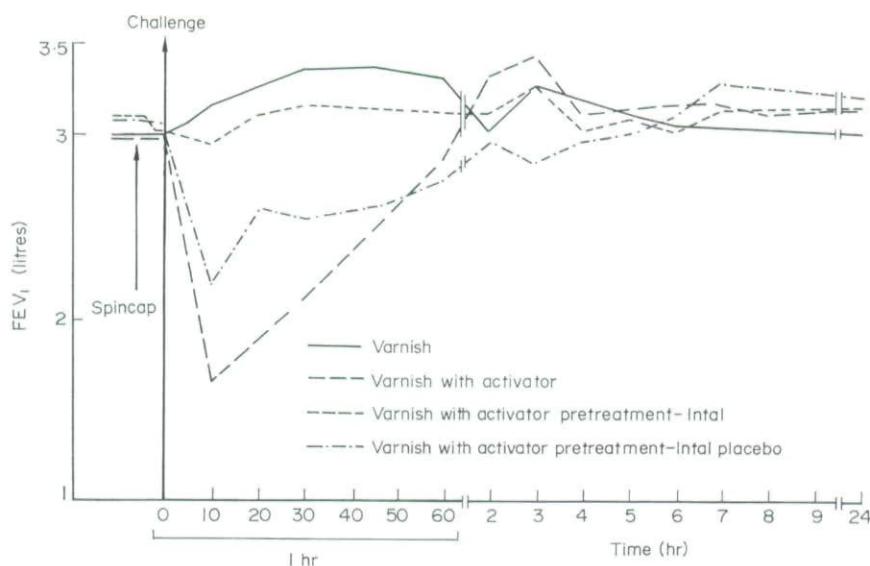


Fig. 3. Patient L.E. Reproducible immediate asthmatic reactions to varnish and 'TDI activator' and inhibition by disodium cromoglycate.

White blood cell count and wet absolute eosinophil counts (in parentheses)

Challenge	Baseline	6-8 hr	24 hr
1	6500 (280)	7600 (400)	
2	7500 (780)	—	
3	11200 (460)	—	
4	9800 (540)	8500 (580)	6400 (370)

3. *Patient D.H.*, a female aged 54, a supervisor in a television factory, first developed chest symptoms 16 months before her attendance in out-patients. Her first symptom was a productive cough followed 2 weeks later by wheezing and breathlessness. This initial episode was diagnosed as bronchitis and treated accordingly. It was 5 weeks before she was able to return to work. Her return was associated with a recurrence of symptoms within 1 week. In the evening following her first day's work, she had sneezing, nasal obstruction and discharge. These symptoms lasted throughout the evening and cleared by the following day. There was no recurrence of rhinitis but after 2 days at work the cough, sputum and breathlessness recurred and rapidly became so severe that she was unable to work. This pattern was repeated every time she attempted to return to work. Major characteristics of her symptoms were their severity and their very prolonged nature, taking 4-6 weeks away from work for complete resolution. She was first seen in out-patients after having returned to work for 2 days, following a 6 week period off work, and as will be seen from her pulmonary function tests at the time she was then suffering from severe asthma.

She had no family or personal history of atopy. She had no significant medical history and had given up smoking 13 years previously.

Occupational history. She was employed for 13 years as a supervisor in a department making parts for up-line transformers, consisting of coil winding and assembly. Her

section was a large bay in which approximately eighty people worked, of whom twelve carried out a soldering process. In this latter process Pope-Venlo wire is dipped firstly into a resin flux and then into multicore solder at a temperature of 460°C. At this point the wire coating is removed by the hot solder and fumes are given off. Each soldering pot has an exhaust hood, but the fumes are exhausted internally into the general atmosphere of the bay itself. The only other ventilation in the bay were its windows which depending on the outside temperature might or might not have been kept open. The Pope-Venlo wire is coated with two resins, one consisting of cured polyurethane and the other of polyvinyl butyral. The main chemical constituent of the resin flux is dimethylamine hydrochloride.

Physical examination. When first seen in out-patients she was severely disabled with asthma. Auscultation demonstrated signs of severe airways obstruction, with widespread inspiratory and expiratory rhonchi and marked prolongation of expiration. Her chest X-ray was normal and pulmonary function tests showed signs of severe airways obstruction.

At this stage, she returned home to rest and after 4 weeks was admitted to hospital for investigation. By this time she was asymptomatic, and physical examination was normal.

Other investigations. Haemoglobin, white blood count and wet absolute eosinophil count were normal. The ESR was elevated with a 29 mm fall in 1 hr. Plasma proteins and electrophoretic strip were normal. Chest X-ray was normal. Skin tests to twenty-three common allergens were negative.

Pulmonary function tests (% predicted)

	Out-patient Department	On admission to hospital 4 weeks later
VC	1380 ml (43%)	3300 ml (97%)
FRC	6550 ml (234%)	3370 ml (120%)
TLC	7650 ml (159%)	5870 ml (122%)
RV/TLC	82%	43.7%
FEV ₁	1450 ml (45.5%)	2380 ml (93%)
FVC	6000 ml (23.5%)	3200 ml (100%)
FEV ₁ /FVC	41.5%	74.5%
CO gas transfer factor (single breath)	12.0 (12.9)	13.2 (9.5)
%CO extraction	46%	37.9%
Airways resistance/LV (body plethysmograph)	2.69 (6320 ml)	1.53 (3240 ml)

Inhalation tests

The following exposure, occupational type, tests were made with:

- (1) Resin flux fumes—three inhalations.
- (2) Amino-ethyl ethanolamine fumes—four inhalations.
- (3) Multicore solder/resin flux/Pope-Venlo wire fumes—10 min exposure.
- (4) Multicore solder/resin flux/uncoated wire—5 min exposure.
- (5) Multicore solder/resin flux/uncoated wire—10 min exposure.
- (6) Polyurethane varnish, mixed with 'TDI activator'—10 min exposure.

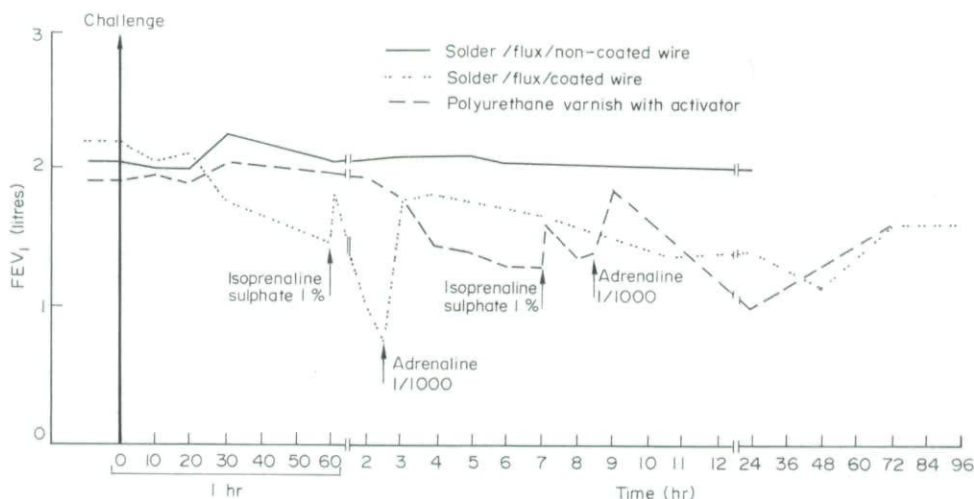


Fig. 4. Patient D.H. No reaction to fumes from noncoated wire. Late asthmatic reactions to fumes from polyurethane coated wire and to the test with varnish plus 'TDI activator.'

Results (Fig. 4)

Tests 1, 2, 4 and 5 gave negative results and there was no marked diurnal variation in pulmonary function tests. None of these tests contained TDI materials. In test 3, in which the polyurethane coating of the wire was present, a marked and prolonged asthmatic reaction was elicited. It started between 30 and 60 min after the end of the exposure. At 2 hr the FEV₁ fell to 55% of pre-test level and an injection of adrenalin resulted in partial reversal of the reaction. She continued to have low grade asthma for 6 weeks before the FEV₁ returned to her pre-test level. In test 6, with the TDI mixed with polyurethane varnish, a late asthmatic reaction was provoked, starting between 3 and 4 hr and reversed by isoprenaline (1%) inhalation after 7 hr. The FEV₁ returned to the pre-test level after 3 days. Sputum collected at 24, 48 and 72 hr after the challenge contained small numbers of cells, with eosinophil percentages of 90, 80 and 1 respectively.

White blood cell count and wet eosinophil count (in parentheses)

Challenge	Baseline	6-8 hr
1	7000 (250)	7500 (150)
2	7600 (280)	7800 (210)
3	6500 (160)	12400 (130)
4	8900 (440)	6600 (180)
5	5300 (90)	6900 (110)
6	6500 (210)	6100 (250)

4. Patient R.U., a female aged 44 years, worked in the same television factory as patient 3 (D.H.). She started soldering wires in 1964 and in 1965 developed a dry cough for the first time. She moved to another part of the same room where she applied sticky tape to coils. Her cough which was dry at first became gradually worse and accompanied by expectoration of three cupfuls of whitish sputum per day. The cough was worse at night and during the week, being better at weekends and

when she was on holiday. She noticed coughing on the way to work which cleared by the time she reached there, only to recur 4 hr after starting work, becoming progressively worse during the day and continuing until late at night. Wheezing first developed in early 1971, coming on about 4 hr after starting work and persisting until she went to bed at night. Wheezing and cough subsequently appeared together.

She was off work for 1 month prior to admission to hospital for investigation.

On examination there were no abnormal physical signs. Prick tests to twenty-three common allergens were negative.

Other investigations. Haemoglobin, white cell count and erythrocyte sedimentation rate were normal. The chest X-ray was normal.

Pulmonary function tests

	Result	% Predicted
VC	3000 ml	97%
FRC	1540 ml	60%
TLC	3740 ml	84%
RV/TLC	40%	
FEV ₁	2600 ml	105%
FVC	3100 ml	100%
FEV ₁ /FVC	84%	
CO gas transfer factor (single breath)	16.7	19.5

Inhalation tests

The following occupational type tests were made with:

- (1) Polyurethane varnish for 30 min.
- (2) Polyurethane varnish mixed with 'TDI activator' for 30 min.
- (3) Inhalation of 20 mg disodium cromoglycate 10 min before challenge with polyurethane varnish mixed with 'TDI activator'.

Results (Fig. 5)

Test 1, with the polyurethane varnish, gave no reaction and there was no marked diurnal variation in the pulmonary function tests. Test 2, with polyurethane varnish plus 'TDI activator', provoked an immediate reaction which resolved by 2 hr and was followed by a late reaction coming on after 3-4 hr, maximal between 5 and 7 hr and with a return to pre-test levels by 24 hr. Test 3 showed that disodium cromoglycate inhibited both immediate and late reactions. Apart from tightness of the chest and cough there were no other reactions and there was no eosinophilia.

White blood cell count and wet absolute eosinophil count (in parentheses)

Challenge	Baseline	6-8 hr
1	5900 (180)	5500 (120)
2	6500 (280)	7000 (190)
3	5700 (180)	NA

Discussion

This simple method of occupational type exposure using the polyurethane varnish with or without a mixture of the 'TDI activator' has shown itself to be a safe, reliable

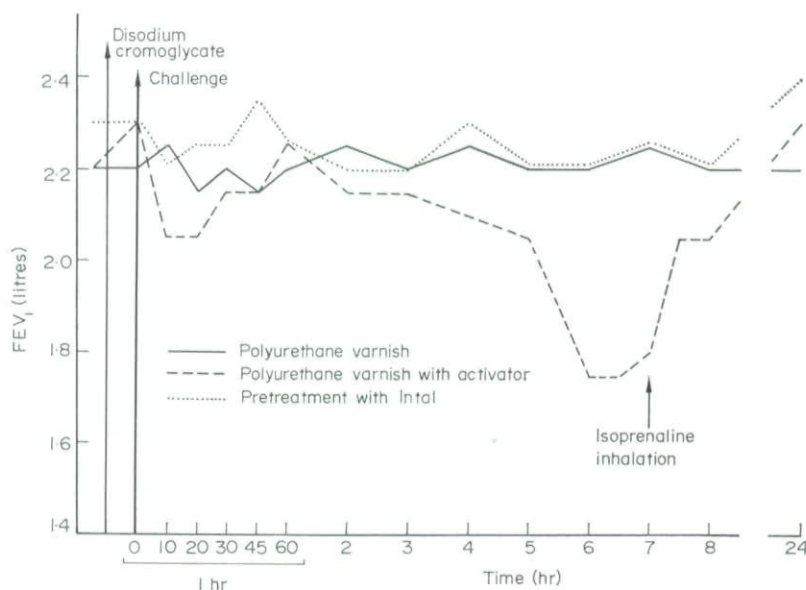


Fig. 5. Patient R.V. No reaction to control test with polyurethane varnish. Immediate and late asthmatic reactions to varnish plus 'TDI activator'. Inhibition of reactions by disodium cromoglycate.

and reproducible method of testing for TDI sensitivity and is therefore of use for clinical confirmation where the TDI is already suspected or for etiological diagnosis where this is not so.

In two of the patients the TDI was encountered in this form in manufacture or in the use of two-pot polyurethane varnish. In the third and fourth cases the possibility of flux asthma (Sterling, 1967; Pickering & Pepys, 1972) was suggested because they were exposed to soldering fumes at work.

As it transpired, after tests in the first patient (3, D.H.) with all the components of the coated wire and flux used at her work, it became evident that the polyurethane coating on the wire was responsible, liberating TDI on heating. This is a hazard of thermoplastic materials sealed by heating. Paisley (1969) drew attention to the isocyanate hazard from wire insulation which he described as 'an old hazard in new guise'. In his case the clinical evidence was sufficiently strong to support the diagnosis. The availability of deliberate occupational type challenges with the TDI in preparations different from those encountered at work adds to the confidence with which etiological diagnosis can be made.

The method employed here seems preferable to the inhalation of an aerosol of TDI mixed with saline which Sweet (1968) employed and which provoked an immediate type asthmatic reaction. The asthma provoked by TDI may be severe and prolonged as seen in Sweet's case and in one of our patients. The very limited nature of the occupational type challenge makes it more acceptable as a mode of inhalation testing. The very small amounts of TDI capable of eliciting reactions is evident from the values of 0.00173–0.0018 ppm found in the air when the varnish plus TDI mixture was being applied as varnish for testing.

The patterns of bronchial reaction elicited showed all three forms, namely immediate asthma, late asthma, and dual asthmatic reactions. Where sputum was available, eosinophil cells were predominant suggesting a reagin, IgE, mediated reaction,

though there were no increases in the absolute eosinophil counts of the blood. There were also no increases in the white cell count or febrile reactions of the sort which have been observed in Type III reactions to fungal and avian allergens (Pepys *et al.*, 1968).

The evidence of reaginic antibody to TDI (Taylor, 1970) and its demonstration against platinum salts in subjects with platinum asthma (Pepys *et al.*, 1972) show that IgE antibody directed against determinants of such small molecular chemical substances are present in sensitized subjects. Other antibodies to isocyanate materials (p-p-diphenylmethane diisocyanate, MDI) have been reported in exposed workers by Konzen *et al.* (1966) using PCA tests in the guinea-pig. These antibodies are probably of the precipitating IgG type, which if complement-fixing could be responsible for the late asthmatic reactions, in the same way that such antibodies are thought to mediate late asthmatic reactions to *A. fumigatus*, avian and other allergens (Pepys, 1969). Other evidence of immunological changes due to the TDI exposure is provided by Bruckner *et al.* (1968) who reported lymphocyte transformation to TDI conjugates in sensitized subjects.

The clinical histories of the subjects reported here and by others (Glass & Thom, 1961; Markham & Fishburn, 1967) are comparable to the reactions to the inhalation tests, in that late asthmatic and nasal reactions were a feature. In some cases further exposure led to the appearance of immediate reactions and in some the histories suggest that dual, immediate plus late reactions, were produced.

The importance of TDI sensitivity in industry is well recognized, though it seems that the concentrations capable of provoking symptoms may be even lower than the 0.01–0.02 ppm thought to be acceptable hitherto. In industry sensitizing exposure is commonly of a much larger order than that likely to be encountered in daily life. The patients reported on here were not subject to heavy exposure and it is possible that sensitization may occur in the increasing exposure to TDI in daily life. Peters & Murphy (1971) draw attention to this forcibly in relation to polyurethane foam 'do it yourself' kits available in hardware stores in U.S.A. These consist of two pressurized cans connected by tubing or of two separate cans with instructions to pour together and then mix. The air samples taken during use of five of these kits showed TDI concentrations of 0.10, 0.21 and 0.04 ppm in three instances. Most of this was given off in the first 10 min of use. They also state that in two subjects, bronchial disease, in one case 'status asthmaticus' was produced shortly after second exposure to these materials. The dangers of polyurethane foams used in so many everyday circumstances when these are exposed to high temperatures must be kept in mind. Glass & Thom (1964) were able to demonstrate TDI levels of 0.6 µg/g in scrap foam on crushing by hand, suggesting that circumstances may arise where it might be liberated into the air under ordinary conditions. The common presence of polyurethane foam materials in daily life make it desirable to test for possible sensitivity to TDI where exposure may have occurred. The hazards of accidental exposure like that of the washing up of drums of TDI on the beaches of Cornwall with the liberation of appreciable amounts, in the present context, into the air also requires consideration. The occupational type exposure described here could serve a very useful role in this regard.

It is also of interest and reflects further on the value of this method of testing that whilst the subjects in this report gave negative reactions to Multicore solder, another asthmatic patient (unpublished) who was exposed to the fumes of this material gave an immediate asthmatic reaction. The causal component in this case has not been identified.

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